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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CRYSTAL STRUCTURES OF DOMAINS OF RECEPTOR PROTEIN TYROSINE KINASES AND THEIR LIGANDS

(57) Abstract: The determination and use of three dimensional structures of receptor protein tyrosine kinases and/or their ligands are described. One particular group of such structures includes three dimensional structures of the extracellular domain of RPTKs. The three dimensional structures of RPTKs can facilitate the design and identification of modulators of RPTK function. Other such structures can include of RPTK ligands, such as stem cell factor or a fragment thereof. Modulators of RPTK function can be used to treat diseases that are mediated by inappropriate RPTK activity.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K14/71 C12N9/12 G06F17/30 C12Q1/37 A61K38/00 G01N33/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K A61K C12Q G01N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PELLEGRINI L ET AL: "The role of heparin in the complex formation between fibroblast growth factor 2 and its high affinity receptor: Comparative modelling and biochemical studies." BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000993500 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 ISSN: 0300-5127 the whole document --- -/--	1-27, 43-51, 54-65, 67-86
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
° Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 26 July 2001		Date of mailing of the international search report 26. 10. 01
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer VAN DER SCHAAL C.A.

INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 00/23744

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>HUHTALA MIKKO T ET AL: "A dimeric ternary complex of FGFR1, heparin and FGF-1 leads to an 'electrostatic sandwich' model for heparin binding." STRUCTURE (LONDON), vol. 7, no. 6, June 1999 (1999-06), pages 699-709, XP000993253 ISSN: 0969-2126 the whole document</p>	<p>1-27, 43-51, 54-65, 67-86</p>
Y	<p>WO 98 07835 A (SCHLESSINGER JOSEPH ;LIANG CONGXIN (US); SUGEN INC (US); TANG PENG) 26 February 1998 (1998-02-26) cited in the application the whole document</p>	<p>1-27, 43-51, 54-65, 67-86</p>
Y	<p>GIVOL DAVID ET AL: "Complexity of FGF receptors: Genetic basis for structural diversity and functional specificity." FASEB (FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY), vol. 6, no. 15, 1992, pages 3362-3369, XP002167375 1992 ISSN: 0892-6638 cited in the application the whole document</p>	<p>1-27, 43-51, 54-65, 67-86</p>
Y	<p>LIEKENS SANDRA ET AL: "Modulation of fibroblast growth factor-2 receptor binding, signaling, and mitogenic activity by heparin-mimicking polysulfonated compounds." MOLECULAR PHARMACOLOGY, vol. 56, no. 1, July 1999 (1999-07), pages 204-213, XP000993567 ISSN: 0026-895X the whole document</p>	<p>58-65</p>
P,X	<p>PLOTNIKOV ALEXANDER N ET AL: "Structural basis for FGF receptor dimerization and activation." CELL, vol. 98, no. 5, 3 September 1999 (1999-09-03), pages 641-650, XP002167376 ISSN: 0092-8674 the whole document</p>	<p>1-27, 43-51, 54-57, 67-86</p>
Y	<p>the whole document</p>	<p>58-65</p>

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PLOTNIKOV ALEXANDER N ET AL: "Crystal structures of two FGF-FGFR complexes reveal the determinants of ligand-receptor specificity." CELL, vol. 101, no. 4, 12 May 2000 (2000-05-12), pages 413-424, XP002167377 ISSN: 0092-8674	1-27, 43-51, 54-57, 67-69, 76-86
Y	the whole document	58-65, 70-75

P,X	PELLEGRINI LUCA ET AL: "Crystal structure of fibroblast growth factor receptor ectodomain bound to ligand and heparin." NATURE (LONDON), vol. 407, no. 6807, 2000, pages 1029-1034, XP002167378 ISSN: 0028-0836	1-4,8, 19-23, 43-51, 67-74,76
Y	the whole document	5-7, 9-18, 24-27, 54-65, 75,77-86

P,X	STAUBER DEBORAH J ET AL: "Structural interactions of fibroblast growth factor receptor with its ligands." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 1, 4 January 2000 (2000-01-04), pages 49-54, XP002167379 Jan. 4, 2000 ISSN: 0027-8424	1-4,8, 19-23, 43-51, 67-74,76
Y	the whole document	5-7, 9-18, 24-27, 54-65, 75,77-86

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 00/23744

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.: **66**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-27, 43-51 and 54-86.

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 68 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 43-51 could be considered as a mere presentation of information or a computerprogram, Rule 39.1(v and vi) PCT, the search has been carried out as far as possible in our systematic documentation

Continuation of Box I.2

Claims Nos.: 66

Present claim 66 relates to a product defined by reference to a desirable characteristic or property, namely modulation of receptor protein tyrosine kinase.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no such product. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method/apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has not been carried out.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 43-51 54-86

Crystals including an extracellular domain of a receptor tyrosine kinase and there use.

2. Claims: 28-42 52 53 87-89

Crystals comprising a receptor binding core of a stem cell factor and there use

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9807835 A	26-02-1998	US 5942428 A	24-08-1999
		AU 733890 B	31-05-2001
		AU 4160397 A	06-03-1998
		EP 0931152 A	28-07-1999
		JP 2001514484 T	11-09-2001
